Lewis Base Catalyzed 1,3-Dithiane Addition to Carbonyl Compounds Using 2-Trimethylsilyl-1,3-dithiane

Makoto Michida[1] and Teruaki Mukaiyama*[1,2]
[1]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*
[2]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

(Received October 16, 2007; CL-071148; E-mail: mukaiyam@abeam.ocn.ne.jp)

1,3-Dithiane addition to various aldehydes and ketones using 2-trimethylsilyl-1,3-dithiane in the presence of a catalytic amount of a Lewis base such as tetrabutylammonium phenoxide (PhON*n*-Bu$_4$) proceeds smoothly to afford the corresponding α-hydroxy dithiane compounds in good to high yields under mild conditions.

Addition reaction of 1,3-dithiane is one of the most important umpolung reactions in synthetic organic chemistry.[1] The dithiane anions are widely known as masked acyl carbanions which react with various electrophiles such as carbonyl compounds to afford the corresponding protected aldehydes. The dithiane group of the above adducts can be deprotected under mild oxidation conditions.[2]

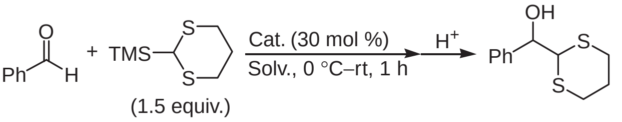
In general, the dithiane addition reaction is carried out by using 1,3-dithiane and an equimolar amount of strong bases such as *n*-butyllithium, and thus-formed lithiated dithiane would behave as a useful nucleophile. 2-Trimethylsilyl-1,3-dithiane (TMS-dithiane) is also used as 1,3-dithiane equivalent and is activated by a stoichiometric amount of fluoride ion such as tetrabutylammonium fluoride (TBAF) or cesium fluoride for the generation of the corresponding carbanion.[3] While most of the reactions are carried out by using an equimolar amount of fluoride reagent, only a few examples on catalytic activation of TMS-dithiane have been reported to date.[4]

These dithiane addition reactions are rather hard to apply to the ketones having α-protons such as acetophenone because of their deprotonation by dithiane anions.[5] Therefore, it is required to find conditions that are milder for the dithiane addition reaction.

In our previous papers, it was shown that the nitrogen- or oxygen-containing anions generated from amides, imides, carboxylic acids, or alcohols behaved as effective Lewis base catalysts in the activation of trimethylsilyl (TMS) derivatives.[6] Also, addition reactions to carbonyl compounds such as aldol reaction, trifluoromethylation, cyanomethylation, and alkynylation had been carried out successfully in the presence of Lewis base catalysts.[7] In this communication, we would like to report an effective method for 1,3-dithiane addition to aldehydes and ketones with TMS-dithiane under mild conditions by using a Lewis base catalyst such as PhON*n*-Bu$_4$.

In the first place, reactions of benzaldehyde with TMS-dithiane were studied in the presence of catalytic amounts of various Lewis bases (Table 1). When AcOLi or AcON*n*-Bu$_4$ was used, the reaction did not proceed (Entries 1 and 2). When a phenoxide anion was employed as a counter anion, on the other hand, it did proceed though the yield of the desired product was low. Effects of counter cations of the phenoxide were further examined, and the yields of the adduct turned to be higher as the nucleophilicities of the anion increased (Entries 3–6). Therefore, the suitable choice of counter cation of phenoxide was crucial to obtain the adducts in high yields, and it was confirmed that ammonium ion gave the best results.[8] Next, the effects of solvents were further examined in the presence of a catalytic amount of PhON*n*-Bu$_4$. Dimethylsulfoxide is also a polar solvent and the corresponding product was afforded in moderate yield (Entry 7). On the other hand, when the reaction was carried out in THF, the yield was very low (Entry 8). It was then found that the TMS-dithiane activation was promoted by polar solvents, and that the best result was obtained when DMF was used.

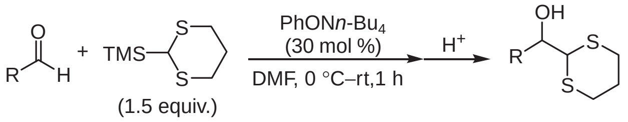
Table 1. Screening of Lewis base catalysts



Entry	Cat.	Solv.	Yield^{a}/%
1	AcOLi	DMF	N.R.
2	AcON*n*-Bu$_4$	DMF	N.R.
3	PhOLi	DMF	16
4	PhONa	DMF	25
5	PhOK	DMF	77
6	PhON*n*-Bu$_4$	DMF	96
7	PhON*n*-Bu$_4$	DMSO	77^{b}
8	PhON*n*-Bu$_4$	THF	14^{c}

^{a}Isolated yield. ^{b}The reaction was carried out at room temperature. ^{c}The reaction was carried out for 2 h.

Table 2. PhON*n*-Bu$_4$-catalyzed dithiane addition to various aldehydes

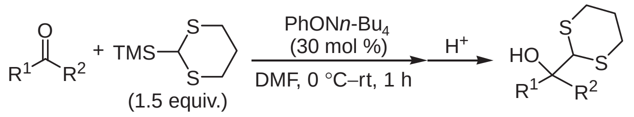


Entry	R	Yield^{a}/%	Entry	R	Yield^{a}/%
1	2-ClC$_6$H$_4$	95	6	2-Furyl	94
2	3-ClC$_6$H$_4$	94	7	3-Pyridyl	80
3	4-ClC$_6$H$_4$	83	8	*t*-Bu	60
4	4-MeC$_6$H$_4$	97	9	*c*-Hex	83
5	4-MeOC$_6$H$_4$	92	10	(*E*)-PhCH=CH	95

^{a}Isolated yield.

Then, reactions of various aldehydes and TMS-dithiane by using a catalytic amount of PhON*n*-Bu$_4$ were tried (Table 2). Aromatic aldehydes having electron-donating or -withdrawing groups and heteroaromatic aldehydes reacted smoothly with TMS-dithiane to afford the adducts in good to high yields (En-

Table 3. PhONn-Bu$_4$-catalyzed dithiane addition to various ketones



Entry	Ketone		Yield[a]/%
	R^1	R^2	
1	Ph	CF_3	93
2	Ph	(E)-PhCH=CH	91
3	Ph	Me	90[b]
4	4-MeOPh	Me	75[b]
5	4-Pyridyl	Me	70
6	(E)-PhCH=CH	Me	75
7	Ph	i-Pr	74[b]
8	c-Hex	Me	63[b]

[a]Isolated yield. [b]50 mol % of catalyst and 3 equiv. of TMS-dithiane was used.

tries 1–7). Similarly, aliphatic aldehydes reacted smoothly as well to afford the desired adduct in moderate to good yields (Entries 8 and 9). When α,β-unsaturated aldehyde was used, only 1,2-addition product was obtained in high yield (Entry 10). Since dithiane adducts were the mixture of their TMS ether and desilylated alcohol in most cases, thus a complete hydrolysis by treating the mixture with 1 M HCl in a short time is necessary for obtaining the corresponding alcohols.

In order to extend the utility of this reaction, use of various ketones as electrophiles was next examined (Table 3). It was then found that this addition to ketones were achieved under the optimized conditions and afforded the corresponding tertiary alcohols. As shown in Entry 1 in which ketones have no protons at α-position, the reaction proceeded smoothly to afford the adducts in high yields. 1,2-Addition products were also obtained in good to high yields when α,β-unsaturated ketones were employed (Entries 2 and 6). Importantly, the reaction of the substrate having α-protons reacted to afforded the desired adduct in moderate to good yields (Entries 3–8). The above results indicated that the nucleophilic addition reaction took place prior to the deprotonation.

Thus, an efficient 1,3-dithiane addition reaction between carbonyl compounds and TMS-dithiane in the presence of Lewis bases proceeded smoothly to afford the α-hydroxy dithiane in good to high yields. It is noted that TMS-dithiane was activated in the presence of a catalytic amount of PhONn-Bu$_4$ in polar solvent such as DMF. Also, this reaction is applicable to the ketones having α-protons as electrophiles. Further studies on this type of reactions are now in progress.

References and Notes

1 a) E. J. Corey, D. Seebach, *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. b) E. J. Corey, D. Seebach, *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077. c) E. T. Corey, D. Seebach, R. Freedman, *J. Am. Chem. Soc.* **1967**, *89*, 434. d) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231. e) B.-T. Gloebel, D. Seebach, *Synthesis* **1977**, 357.

2 a) *Protective Groups in Organic Synthesis*, 3rd ed., ed. by Theodora. W. Greene, Peter. G. M. Wuts, Wiley-Interscience, Canada, **1991**, p. 336. b) H. Firouzabadi, N. Iranpoor, H. Hazarkhani, B. Karimi, *J. Org. Chem.* **2002**, *67*, 2572. c) N. Iranpoor, H. Firouzabadi, H. R. Shaterian, *Tetrahedron Lett.* **2003**, *44*, 4769. d) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192. e) B. Karimi, H. Hazarkhani, *Synthesis* **2003**, 2547.

3 a) J. Busch-Petersen, Y. Bo, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 2065. b) A. Capperucci, V. Cerè, A. D. Innocenti, T. Nocentini, S. Pollicino, *Synlett* **2002**, 1447.

4 A. S. Pilcher, P. DeShong, *J. Org. Chem.* **1996**, *61*, 6901.

5 N. H. Andersen, D. A. Mccrae, D. B. Grotjahn, S. Y. Gabhe, L. J. Theodore, R. M. Ippolito, T. K. Sarkar, *Tetrahedron* **1981**, *37*, 4069.

6 a) H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2002**, 182. b) H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2002**, 858. c) H. Fujisawa, T. Nakagawa, T. Mukaiyama, *Adv. Synth. Catal.* **2004**, *346*, 1241. d) T. Mukaiyama, T. Nakagawa, H. Fujisawa, *Chem. Lett.* **2003**, *32*, 56. e) T. Mukaiyama, T. Tozawa, H. Fujisawa, *Chem. Lett.* **2004**, *33*, 1410. f) H. Fujisawa, E. Takahashi, T. Nakagawa, T. Mukaiyama, *Chem. Lett.* **2003**, *32*, 1036. g) E. Takahashi, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2004**, *33*, 1426.

7 Aldol reaction: a) Y. Kawano, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 614. Trifluoromethylation: b) T. Mukaiyama, Y. Kawano, H. Fujisawa, *Chem. Lett.* **2005**, *34*, 88. Cyanomethylation: c) Y. Kawano, N. Kaneko, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1508. Alkynylation: d) T. Kitazawa, T. Minowa, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 1002.

8 Typical experimental procedure is as follows (Table 1, Entry 6): To a stirred solution of PhONn-Bu$_4$ (50.3 mg, 0.15 mmol) and benzaldehyde (53.1 mg, 0.50 mmol) in DMF (1.5 mL) were added 2-trimethylsilyl-1,3-dithiane (142 µL, 0.75 mmol) at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 1 h and quenched with 1 M HCl (1.0 mL, 1.0 mmol). The mixture was extracted with EtOAc and organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC (hexane/EtOAc = 2/1) to give the desired product (109.2 mg, 96%) as a white crystal.